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(54) **Use of estrogen antagonists and estrogen agonists in inhibiting pathological conditions**

Verwendung von Östrogenantagonisten und - agonisten zur Hemmung pathologischer Zustände

Utilisation des antagonistes et agonistes de l'oestrogène pour l'inhibition des conditions pathologiques

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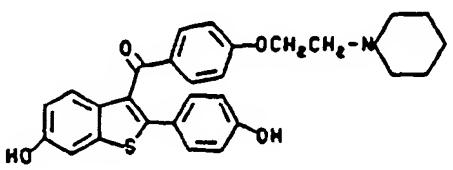
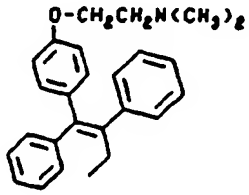
Description

BACKGROUND OF THE INVENTION

[0001] Certain estrogen agonists have been reported to be useful in inhibiting pathological conditions related to organ systems which respond to estrogen agonists or antagonists. In particular, 2-phenyl-3-aroylbenzothiophenes and 1-(alkylaminoethoxy phenyl)-1 -phenyl-2-phenylbut-1-enes represented by raloxifene and tamoxifen have wide application as estrogen agonists.



Raloxifene



Tamoxifen

Raloxifene has been claimed to be effective in the treatment of acne, U.S. 5,439,923; alopecia, EP 0659414 A2; Alzheimers disease, EP 0659418 A1; atrophy of skin and vagina, US 5,461,064; auto immune disease, EP 0664123; breast cancer, US 4,418,068; breast disease, EP 0659419; cartilage degeneration, US 5,418,252; CNS problems (post menopausal), 94 EP 0309470; pathology of endocrine target organs, US 4,418,068; delayed puberty, US 5,451,589; demyelinating disease, US 5,434,166; dysmyelinating disease, US 5,434,166; dysmenorrhea, US 5,446,053; endometriosis, US 5,461,065; female infertility, EP 659429 A1; fertility disorders; hirsutism, EP 0659414 A2; hypoglycemic, EP 635264 A2; increase libido, US 5,439,931; inhibition of fertility, US 5,462,949; LDL oxidation, EP 0664121 A; hypercholesterolemia, US 5,464,845; lupus erythematosus, EP 0664125; impaired macrophage function, EP 659425 A1; male infertility, EP 0659424 A1; myocardial infaction, ischaemia, thromboembolic disorder, thrombin inhibition, EP 0664126; menopausal disorders, EP 0659415; menstruation disorders, US 5,462,950; obesity, 94 EP 0309481; obsessive compulsive disorder, EP 0659428; osteoporosis, US 5,457,117; ovarian dysgenesis, US 5,451,589; peri-menopausal syndrome, US 5,391,557; peripheral vasoconstriction, US 5,470,883; post menopausal CNS, EP 0659415; premenstrual syndrome, US 5,389,670; prostatic carcinoma; prostatic hyperplasia; pulmonary hypertension, US 5,447,941; reperfusion damage, J. AM. Cardiol 25, 189A (1993); resistant neoplasm, EP 0652004 A1; restenosis, US 5,462,937; rheumatoid arthritis, EP 0664125; seborrhea, US 5,439,923; sexual dysfunction; sexual precocity, US 5,451,590; thrombomodulin expression, EP 0659427; Turners syndrome, US 5,441,966; uterine fibrosis US 5,457,116; and vasomotor symptoms (post menopausal), 94 EP 0309473.

[0002] Tamoxifen is widely employed in the treatment of breast cancer and has been reported to be effective in the treatment of the following diseases and conditions: high lipid levels, Drug Ther. 22/3, 109 (1992); ovarian cancer, J. Clin. Oncol. 11, No. 10, 1957-68 (1993); renal cell carcinoma, Br. J. Radiol 56, No. 670, 766-7 (1983); suppression of atherogenic factor homocysteine, Env. J. Cancer 29 Suppl. 6, S110 (1993); metastatic melanoma, J. Clin. Oncol. 12, No. 8, 1553-60 (1994); mastalgia, Drugs 32, No. 6, 477-80, (1986); prolactive secreting pituitary tumors, J. Endrocrinol. Invest. 3/4, 343-347 (1980); osteoporosis, Proc. Annu Meet Am Assoc. Cancer Res.; 33: A566-7 (1992); netroperitoneal fibrosis, Lancet 341, No. 8841, 382 (1993).

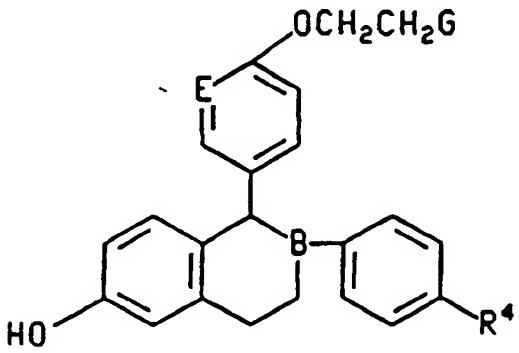
[0003] Small structural changes in the structure of estrogen agonists cause profound differences in biological properties. For example, droloxifene (3-hydroxytamoxifen) has a 10-60-fold higher binding affinity to the estrogen receptor compared to tamoxifen. Droloxifene is devoid of in vivo or in vitro carcinogenic or nutagenic effects, whereas tamoxifen causes liver tumors in rats. Hasmamu, et al. Cancer Letter 84, 101-116 (1994).

[0004] Droloxifene has been reported to be effective in the treatment of breast cancer US 5,047,431; endometriosis, US 5,455,275; lowering cholesterol, US 5,426,123; osteoporosis, US 5,254,594; prostatic hyperplasia, US 5,441,986; and restenosis, US 5,384,332.

SUMMARY OF THE INVENTION

[0005] The present invention provides the use of an effective amount of a compound of formula I for the manufacture of a medicament for inhibiting a pathological condition which is susceptible or partially susceptible to inhibition by an antiestrogen or estrogen agonist, said pathological condition being selected from the group consisting of uterine cancer,

migraine, incontinence, bladder infection, senile gynecomastia, diabetes, hyperglycemia, failure of wound healing, melanoma, impotence, inflammatory bowel disease, decreased libido, immune system disord rs, pulmonary hypertensive disease, s borrhea, Turner's syndrome, alopecia and obsessive-compulsive disorders, Compound of formula I



I

wherein G is

and
R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N.

[0006] Especially preferred compunds are:

Cis-6-(4-fluoro-phenyl)-5-[4-(2-plperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol;
(-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol;
Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalen-2-ol;
Cis-1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene;
1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;
Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol; and
1-(4'-Pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

DETAILED DESCRIPTION OF THE INVENTION

[0007] The present invention is related to methods for inhibiting pathological conditions which are susceptible or partially susceptible to inhibition by an estrogen, antiestrogen or estrogen agonist. Such conditions include uterine cancer. migraine, incontinence, bladder infection, senile gynecomastia, diabetes, hyperglycemia, failure of would healing, melanoma, impotence, inflammatory bowel disease decreased libido, Immune system disorders, pulmonary hypertensive disease, seborrhea, Turner's syndrome, and obsessive-compulsive disorders.

[0008] Changes In the appearance and texture of the skin with Increasing age has been proverbial and well documented both quantitatively and qualitatively. It is a subject which is highly subjective in its evaluation and its ultimate effect on the individual. By in large the effect of the general atrophy of skin with age is cosmetic, but can have pathological consequences, many of which are psychological in nature, i.e., the feeling of getting "old," depression, loss of sexual attractiveness, etc. In some cases, the atrophy of the skin in older people can have direct pathologies associated with it, e.g., the ability of the skin to repair in wound healing. In general, the atrophy of the skin is considered a normal and progressive consequence of the aging process and taken with "good grace." Despite the normal acceptance of aging, there is a particular time in a woman's life, i.e., the menopause, when the progressive aging pattern is greatly accelerated, especially with regard to atrophy of the skin. It is often this rapid acceleration and suddenness of change which can be contributory to pathological and psychological distress.

[0009] As mentioned before, the atrophy or aging of the skin can have both qualitative and quantitative aspects. The qualitative aspects are: the change of smoothness and texture, thus causing a "roughness" in look and feel on the

outer surface of the skin, the change of elasticity of the skin, thus effecting the mechanical properties of the skin, and the chang s in skin pigmentation. Thes qualitative changes result in the commonly described condition of atrophied skin as: wrinkled, rough, withered, and spotty. Quantitatively, skin aging In post-menopausal women can be measured as: a decrease in the mitotic rate of keratinocytes, changes in dermal thickness, d crease in glycosaminoglycans and soluble collagen which are linked to the moisture content of the skin, and the decrease in the urinary excretion of hydroxyproline, a measure of decrease collagen turnover. The qualitative changes in the skin, i.e., sightl ssness and mechanical properties, are the result of the quantitative changes, i.e., loss or change of the extra-cellular matrix components. Therefore, it is possible to evaluate a beneficial effect of a therapy for post-menopausal skin atrophy without totally relying on subjective analysis, even though a subjective improvement may be the ultimate desired effect. In the case of vaginal atrophy, the quantitative aspect is the amount of vaginal moisture which is controlled by the amount of secretion from glands in the dermis, the qualitative result is subjective comfort.

[0010] Currently, there are two major therapies available for the treatment of skin and vaginal atrophy in post-menopausal women. The first therapy is strictly a cosmetic approach, e.g., the use of make-up, skin moisturizers, night cremes, vaginal lubricants, etc. Although this cosmetic therapy does not affect the underlying physiological cause of the atrophy, often it does achieve some subjective benefit for the individual. The second type of therapy involves the treatment of the underlying physiological causes with active, medicinal agents, most notably Vitamin A and estrogens. Vitamin A is used, its effectiveness is controversial, and it is known to have substantial, undesirable side-effects which limit its use.

[0011] At the time of menopause, the levels of estrogen produced by the ovaries rapidly decrease. This decrease in estrogen has pronounced effects on the skin and vagina causing a rapid acceleration in the natural process of atrophy. Estrogen replacement therapy is often beneficial in treating skin and vaginal atrophy. However, estrogen replacement therapy has undesired side-effects, most serious of which is the potential for the development of the threat of cancer. The inclusion of progestinal agents leads to undesirable psychological effects. The use of estrogen replacement therapy for the sole purpose of treating skin and vaginal atrophy is not common because of the negative side-effects. Clearly, an effective and safe agent which positively effects the underlying physiology and thus improves the qualitative aspects of skin and vaginal properties in post-menopausal women would be useful.

[0012] Due to the advancements in medical science, along with education, the quality and length of life have both been increased. As a result, the population, as a whole, is living longer. As such, situations which have been present but not in great numbers are becoming more numerous and recognized.

[0013] One of those situations which has been present but possibly not given enough weight is sexuality In old age. While there has always been some thought that old people are incapable of engaging in sexual activities, which Is somewhat supported by a definite decline in sexuality for both sexes as they get older, sexual activity among the elderly cannot be ignored. Therefore, problems associated with such activity also cannot be ignored.

[0014] While the male, from the early and middle years, has a relatively steady decline in sexual capacity and activity, the same cannot be as convincingly said about women. There are reports that the sexual capacity of the female does not change much until late in life. (Kinsey, A.C., et al., Sexual Behavior In the Human Female, Saunders, PA., pg. 353 (1953)). In particular, libido decreases substantially in a considerable percentage of cases after the menopause (Lauritzen et al., Estrogen Therapy the Benefits and Risks, 3rd International Workshop on Estrogen Therapy in Geneva, Oct. 20-21, 1977, Frontiers of Hormone Research, Vol. 5, pg. 10 (1978)). This belief is supported by Pfeiffer, E., et al., Terminus of Sexual Behavior in Middle and Old Age; Journal of the American Geriatric Society, pg. 2151-2158 (1972), and Pfeiffer et al., Sexual Behavior in Middle Life, American Journal of Psychiatry, 128, 1262-1267 (1972). In the Pfeiffer studies, a much greater decline in both sexual activity and interest among women between the ages of 45 and 71 was found as compared to men the same age, and the most dramatic change took place between 50-60 years of age, which is, of course, generally the period during which women experience menopause or are post-menopausal. In the age group of 66-71, 50% of women said they had no or little sexual interest compared with 10% of men in the same age group.

[0015] While there has been no direct link between declining estrogen levels and declining sexuality, it has been stated that hormonal changes following a natural menopause, and certainly following surgical menopause, may contribute to the sexual decline in a portion of women. Exactly how menopause contributes to the loss of libido is not understood, yet seems fairly evident. (Bancroft, Human Sexuality and Its Problems, 2nd ed., pg. 292-293, (1989)). Therefore, it would be of use to find compounds which increase libido In post-menopausal women.

[0016] Pulmonary hypertension represents a serious, life threatening spectrum of diseases of multiple etiology. These include congenital abnormalities of the lung, thorax and diaphragm, congenital or acquired valvular or myocardial disease, obstructive lung disease, and can be a complication of autoimmune diseases, vasculitis and collagen based diseases (Rubin, Chest. 104: 236, 1993). Patients with pulmonary hypertension frequently present with symptoms including dyspnea, fatigue, syncope, and chest pain, and have increased pulmonary artery pressure and demonstrate prominence of the main pulmonary artery, hilar vessel enlargement and decreased peripheral vessels on chest radiographs (Rich. Ann. Intemal. Med., 107: 216, 1987).

[0017] While pulmonary hypertension has multiple etiologies, primary pulmonary hypertension appears to involve an autoimmune component and has been reported as a complication in pati nts with mixed connectiv tissue dis as , rheumatoid arthritis, Sjogren's syndrome, systemic sclerosis and lupus (Sato, Hum. Path, 24: 199, 1993). Primary pulmonary hypertension occurs In f males 1.7 times more frequently than males with the greatest predominanc between the third and fourth decades of life (Rich, Ann. Internal. Med., 107: 216, 1987). The increased incidence of primary pulmonary hypertension in women of child bearing age as well as the clinical observations that the diseas can be exacerbated by pregnancy and oral contraceptives (Miller, Ann. Rheum. Dis. 46: 159, 1987; and cited in Farhat et al., J. PET., 261: 686, 1992) suggests a role for estrogen in the disease process. To this extent, Farhat et al. have demonstrated that estradiol potentiates the vasopressor response to a thromboxane mimetic in perfused rat lungs (J. PET, 261: 686, 1992). However, the role of estrogen in pulmonary hypertension is complex and may be dependent on the etiology of the disease process. In a rat model of pulmonary hypertension induced by injection of monocrotaline pyrrole (Reindel, Tax, Appl. Pharm., 106: 179, 1990) progressive pulmonary hypertension, right ventricular hypertrophy and interstitial edema around the large airways and blood vessels becomes apparent, similar to the pathology observed In man. Estradiol treatment decreased right ventricular hypertrophy and prevented interstitial edema in this model (Farhat et al., Br. J. Pharm., 110: 719,1993) as well as attenuating the hypoxic vasoconstrictive response in isolated sheep lungs (Gordon et al., J. Appl. Physiol., 61: 2116, 1986).

[0018] Current therapy for pulmonary hypertension is inadequate and is largely dependent on the use of vasodilators, diuretics, and anticoagulants (Rubin, Drugs, 43: 37, 1992; Palevsky, JAMA, 265:1014, 1991). Vasodilators are effective in only a small subpopulation of patients with primary pulmonary hypertension and is complicated by systemic hypotensive responses. Prostacyclin infusion and high dose calcium channel blockers are also being used with limited efficacy. Heart-lung and single lung transplantation have been used on patients which do not respond to vasodilator therapy, however, due to surgical morbidity and mortality, this approach is usually limited to those patients who continue to deteriorate despite aggressive therapy at centers experienced in management of this disease. Patients frequently die of right heart failure and those individuals which have signs of right heart failure have a mean survival of 6-12 months (Rubin, Drugs, 43: 37, 1992).

[0019] Therefore, pulmonary hypertensive diseases are characterized by inadequate therapies, necessity of organ transplantation and poor prognosis, and a need exits for new therapies.

[0020] Seborrhea is a general classe of skin disease which is marked by an abnormal function (usually hyperactivity) of the sebaceous glands in the skin. The subject of this invention is the use of compounds to inhibit seborrhea.

[0021] Seborrhea or seborrheic dermatitis is a group of skin diseases thought to be associated with abnormal function of the sebaceous glands. it occurs in areas where there are large numbers of sebaceous glands and is characterized by flasking of the skin and red, mildly Inflammatory patches. Seborrhea is most common in the hair (a form of dandruff), scalp margins, eyebrows, naso-labial folds, external ear canals, postier auricular fold, and prestemal area. Generally, mild seborrhea is controlled by topical medication such as glucocorticoids and LDH in Nivea oil. However, more severe cases are more difficult to control.

[0022] There are several conditions in which the ovaries do not develop and in consequence puberty does not occur. Gonadal dysgenesis results in a severe disease state known as Turner's Syndrome resulting from the absence of a second sex chromosome (X chromosome monosomy). The syndrome is associated with the female phenotype, shortness of stature, sexual infantilism, and various somatic abnormalities. Several typical features are observed in these patients including distinct facial features, square chest, and short broad neck with webbing. Additional anomalies include cubitus valgus, congenital lymphedema of the feet and hands, renal abnormalities, high arched palate, skeletal anomalies, pigmented nevi, keloid formation, abnormal nails, and recurrent otitis media. Cardiovascular abnormalities include bicuspid aortic valves, partial anomalous venous drainage, and hypoplastic left-sided heart syndrome (Miller, M.J., et al. J. Pedriatr., 102: 47-50, (1983), Mazzanti, I. et al. Helv, Paediatr. Acta, 43: 25-31, (1988), Van Egmond, H. et al. Br. Heart J., 60: 69-71, (1988)). Renal abnormalities include rotation of the kidney, horseshoe kidney, duplication of renal pelvis and ureter, and hydronephrosis secondary to ureteropelvic obstruction.

[0023] Skeletal maturation is normal or slightly delayed in childhood but lags in adolescence as a result of gonadal steroid deficiency. Typically, fishnet appearance caused by localized rarefications occurs. Bone mineral content reduction occurs as early as 8 years of age as well as later in puberty. Changes of the spine, vertebral hypoplasia, and scoliosis are also common. Abnormalities of the carpal, wrist, knee and pelvis are also noted. The shortness of stature, including uterine growth retardation, is not evident until after the first 3 years of life after which growth velocity decelerates appreciably (Park, E., et al. Pediatr. Res. 17: 1-7, (1983), Lyon, A. J. et al. Arch. Dis. Child., 60: 932-935, (1985)). In general, the patients suffer from sexual infantilism with genital ducts and external genitalia being immature. As a result, ovarian development is retarded.

[0024] Current therapy is directed towards correcting stature, somatic anomalies and inducing secondary sexual characteristics. Recent data indicated growth hormone is a viable therapy for stature improvement (Rosenfeld, R. G., et al. J. Pediatr., 113: 393 (1988)). Patients not treated with estrogen often develop a severe form of osteoporosis similar to that experienced by females after menopause. Fractures and vertebral collapse are common. Steroid hor-

mone therapy is normally deferred until after 15 years of age as it is believed treatment at an earli r ag may result in prematur maturation of the skeleton and thus a decrease in height. In fact, pharmacological doses of estrogen can accelerate bone maturation and resulting in epiphyseal fusion at an early age without concomitant increases in height. Other studies have shown low-dose estrogen allows patients to develop breasts without causing any changes in h ight (Alexander, R.L. et al., Clin. Res. 26: 174A (1978)). However, studies indicate a number of cases of endometrial cancer in patients with gonadal dysgenesis as a result of estrogen therapy (Levine, L.S., P diatrics, 62: 1178-1183 (1979)).

[0025] Given the adverse side effects of estrogen in Turner's Syndrome patients, a need exists for a bone sparing agent which does not posses significant uterotrophic consequences.

[0026] Diabetes mellitus Is a systemic disease characterized by disorders In the actions of insulin and other regulatory hormones in the metabolism of carbohydrates, fats and proteins, and in the structure and function of blood vessels. The primary symptom of diabetes is hyperglycemia, often accompanied by glucosuria, the presence in urine of large amounts of glucose, and polyuria, the excretion of large volumes of urine. Additional symptoms arise in chronic or long standing diabetes. These symptoms include degeneration of the walls of blood vessels. Although many different organs are affected by these vascular changes, the nerves, eyes and kidneys appear to be the most susceptible. As such, long-standing diabetes mellitus, even when treated with insulin, is a leading cause of blindness.

[0027] There are two recognized types of diabetes. Type I diabetes is of juvenile onset, ketosis-prone, develops early In life with much more severe symptoms and has a near-certain prospect of later vascular involvement. Control of this type of diabetes is difficult and requires exogenous insulin administration. Type II diabetes mellitus is of adult onset, ketosis-resistent, develops later in life, is milder and has a more gradual onset.

[0028] One of the most significant advancements In the history of medical science came in 1922 when Banting and Best demonstrated the therapeutic effects of insulin in diabetic dogs. However, even today, a clear picture of the basic biochemical defects of the disease is not known, and diabetes remains a serious health problem. It is believed that two percent of the United States' population is afflicted with some form of diabetes. The introduction of orally effective hypoglycemic agents was an important development in the treatment of hyperglycemia. Oral hypoglycemic agents are normally used in the treatment of adult onset diabetes.

[0029] Observations in animal models on glucose metabolism for type II diabetes and in humans suggest that sex steroids play a permissive role in the phenotypic expression of hyperglycemia. These observations have prompted studies on the effects of androgens and estrogens on blood glucose levels. Testosterone administration to intact or ovariectomized female rats resulted In marked insulin resistance which correlated to morphological changes in muscle, Holmang, et al., Am. J. Physiol., 259, E555-560 (1990); Holmang, et al., Am. J. Physiol., 262, E851-855 (1992). In streptozotocin diabetic rats, implanted testosterone antagonized the ability of residual insulin to maintain glycemic control, Le et al., Endocrinology, 116, 2450-2455 (1985). In contrast, glucosuria disappeared in castrated diabetic KK mice and reappeared when androgens were replaced in these mice, Nonaka, et al., Jpn. J. Vet. Sci., 50, 1121-1123 (1988): Higuichi, et al., Exp. Anim., 38, 25-29 (1989).

[0030] Results from estrogen administrations also support the hypothesis that the balance between androgens and estrogens is critical to the development of hyperglycemia. Daily estradiol administrations to diabetic KK mice normalized the blood glucose levels and eliminated glucosuria, Toshiro, et al., Jpn. J. Vet. Sci., 51, 823-826 (1989). Estradiol also lowered the blood glucose levels of C57BL/6J-ob/ob mice, Dubuc, Proc. Soc. Exp. Biol. Med., 180, 468-473 (1985) and C57BL/KsJ-db/db mice, Garris, Anatomical Record, 225, 310-317 (1989).

[0031] In climacteric women, anxiety, depression, tension and irritability begin during the perimenopause and can be correlated to reduce estrogen levels and estrogen replacement therapy has been recommended for the treatment of these symptoms (Malleson J., Lancet, 2: 158, (1953); Wilson et. al., J. Am. Geriatric Soc., 11: 347 (1963)). The mechanism for protective effects of estrogen in this case in unknown, but may be related to potential effects of estrogen on biogenic amines such as serotonin (Aylward M., Int. Res. Communications System Med. Sci., 1: 30 (1973)). To this regard circulating serotonin is reduced in post-menopausal women (Gonzales G., et. al., Maturitas 17: 23-29 (1993)), and serotonin (as well as several other biogenic amines) have a putative role in behavioral depression.

[0032] Phillips and Sherwin (Psychoneuroendocrinology, 17: 485-495 (1992)) reported that in surgically menopausal women given estrogen, scores in immediate and delayed recall tests are greater than in similar women not given estrogen. Two potential hypotheses might explain this effect. There is some evidence that partial estrogen agonists (or anti-estrogens) such as tamoxifen interact with the muscarinic receptor (Ben-Baruch G., et. al., Molec. Pharmacol. 21: 287-293 (1982)), and muscarinic agonists (M_2) are known to produce positive effects in a number of memory associated tasks and may have clinical relevance in Alzheimer's Disease. Another interesting possibility may be linked to neurokinins such as Substance P, which are known to have neurotrophic as well as memory-promoting effects (Thoenen H., Trends in Neuroscience, 14: 165-170 (1991); Huston J. et. al., Neurosci. Biobehav. Rev. 13: 171-180 (1989)), thus, through an effect either at a neurotransmitter receptor in the CNS or at a neuropeptide receptor, a tissue selective estrogen agonist/antagonist could produce memory and cognitive enhancing effects. Such an activity would most relevantly be assessed in man, but a variety of animal models (i.e. maze learning, extinction etc.) are available for preclinical testing.

[0033] Perhaps the most frequent CNS related problem in climacteric women is the occurrence of hot flushes. While this undoubtedly Is a somatic effect mediated by effects on the microvasculature, current evidence points strongly in the direction of CNS initiated effect (Lomax P., et. al., Pharmac. Th r. 57: 347-358 (1993)). Therefore, a tissue selective estrogen agonist/antagonist might offer the ideal therapy providing the desired effect in the absence of untoward side effects on reproductive tissue.

[0034] Obsessive-compulsiv disorder is one of the rarer psychiatric illnesses, although minor obsessional symptoms probably occur in one-sixth of the population (Encyclopedia of Medicine, American Medical Association; Current Diagnosis, W.B. Saunders Company, 1985). It is characterized by one or both of two symptoms. The first comprises recurrent, intrusive ruminative thoughts that the patient may realize are senseless but of which he cannot stop thinking. The most common of these are thoughts of violence, contamination, doubt, or personal illness. Normally, the patient does not believe these thoughts are true reflections of reality. However, some patients become convinced that their obsessive ruminations are true, and suffer from psychotic delusions.

[0035] The second comprises repetitive, ritualistic behaviors that the patient recognizes are needless but that he cannot keep himself from performing. Hand washing, counting, checking rituals, and touching rituals are examples of such rituals. The carrying out of the ritual is not constant, but fluctuates and mirrors anxiety levels. There normally are intense feelings of panic and anxiety if the patient is prevented from completing a ritual.

[0036] While appearing depressed, a review of the history of obsessive-compulsive patients normally reveals that obsessions and compulsions precede the onset of dysphoric mood states and that depressed feelings are related to the impact the obsessive-compulsive behavior has on life. In severe cases, the patient will be incapacitated, completely overtaken by the distraction of constant obsessive ruminations or the demand to complete endless compulsive rituals.

[0037] This invention is related to methods for inhibiting obsessive-compulsive disorders.

[0038] Alopecia (hair loss) can occur in women for a variety of reasons, and includes female pattern alopecia. Female pattern alopecia is characterized by chronic and progressive hair loss often beginning around thirty years of age and accelerating at menopause. The hair loss is usually confined to the central scalp in a diffuse pattern. This loss of hair is cosmetically damaging and often psychologically disturbing to the patient. The etiology of the condition has been linked to an elevated level of androgens and the subsequent response of androgen sensitive hair follicles. Treatment of the condition is primarily cosmetic in nature, e.g., wigs, hair styles which cover the effected area, etc. The drug, Spironolactone, has been used, but does have side-effects. Clearly, an effective treatment for this condition would be useful.

[0039] Macrophages play a central role in host defense through a variety of effector mechanisms involving both membrane related and secretory events (Gordon et. al., Curr. Opin. Immunol., 4, 25, 1992; Fuller, Brit. Med. J., 48, 65, 1992). Phagocytosis, chemotaxis and antigen presentation are membrane related processes involved in immunologic defense mechanisms necessary for host survival. The importance of macrophages in defense against microbes, immune surveillance, destruction of tumor cells, and in the clearing of senescent erythrocytes has been documented in man and in animal models characterized by the selective elimination of macrophages (Claassen et. al., J. Immunol Meth., 134, 153, 1990). Macrophages also contribute to host defense through secretion of bacteriostatic and bactericidal proteins, cytokines and lipid mediators, as well as oxygen and nitrogen reactive intermediates. The secretory capacity of the macrophage Is central to its function as these cells secrete over 100 distinct mediators and are located in every organ (Nathan, J. Clin. Invest., 79, 319, 1987).

[0040] While aberrant activation of macrophage functions is associated with autoimmune diseases as well as both chronic and acute inflammatory processes, the reciprocal condition, suppression of macrophage effector functions, is associated with reoccurring infections of both opportunistic and non-opportunistic pathogens and contributes to increased morbidity and mortality. Populations associated with an immunocompromised state include bum patients, transplants, HIV infected individuals, cancer patients undergoing chemotherapy and surgical patients, notably those with a higher risk of infection as observed in thoracoabdominal patients.

[0041] Current therapeutic approaches to these patients includes the use of intravenous infusion of macrophage derived cytokines notably the colony stimulating factors G-CSF, GM-CSF, and M-CSF (Nemunaitis, Transfusion 33: 70, 1993). Supportive therapy with antibiotics and fluids is also used, however, the limitations of these approaches are demonstrated by the continued problems of infection in immunocompromised patients and the emergence of more deadly strains of antibiotics resistant organisms. Furthermore, infections of immunocompromised patients with opportunistic pathogens including Pneumocystis and Cryptococcal infections remain significant and result in complications despite various antibiotic protocols. Clearly, novel therapeutics which can selectively enhance macrophage effector functions to augment host defense would play a central role in the clinical management of these patients.

[0042] Estrogen has been reported to increase select macrophage effector functions including Fc mediated phagocytosis, class II antigen expression, and IL-1 secretion. These observations coupled with the known propensity of women to be more resistent to a variety of infections (Ahmed et al., Am. J. Path., 121, 531, 1985) suggests that estrogen-like compounds may enhance macrophage effector functions and thus be beneficial in disease states associated with depressed host defense such as bladder infections or depressed wound healing.

[0043] The term "inhibit" is defined to include its generally accepted meaning which includes prophylactically treating a subject to prevent the occurrence of one or more of these disease states, holding in check the symptoms of such a disease state, and/or treating such symptoms. Thus, the present methods include both medical therapeutic and/or prophylactic treatment, as appropriate.

[0044] Compounds of formula I are described as being effective in treatment of prostate disease, osteoporosis, endometriosis, cardiovascular disease and hypercholesterolemia in commonly own d United States Pat nt application serial no. 08/369,954 which published as WO 96/21656 on 18th July 1996.

[0045] Estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissues.

[0046] Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions -of estrogen in one or more tissues.

[0047] One of ordinary skill will recognize that certain substituents listed in this invention will be chemically incompatible with one another or with the heteroatoms in the compounds, and will avoid these incompatibilities in selecting compounds of this invention. Likewise certain functional groups may require protecting groups during synthetic procedures which the chemist of ordinary skill will recognize.

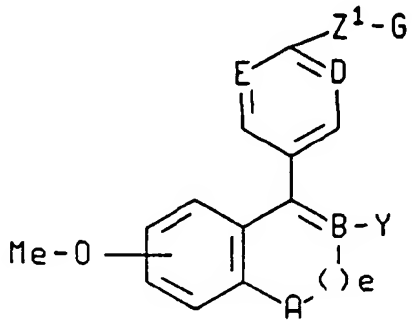
[0048] The chemist of ordinary skill will recognize that certain compounds of this invention will contain atoms which may be in a particular optical or geometric configuration. All such isomers are included in this invention; exemplary levorotatory isomers in the cis configuration are preferred. Likewise, the chemist will recognize that various pharmaceutically acceptable esters and salts may be prepared from certain compounds of this invention. All of such esters and salts are included in this invention.

[0049] The remedies for the conditions and diseases for use in the methods of this invention can be prepared by the methods commonly employed using conventional, organic or inorganic additives, such as an excipient (e.g., sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder (e.g., cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylprrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose or starch), a disintegrator (e.g., starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant (e.g., magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent (e.g., citric acid, menthol, glycine or orange powder), a preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer (e.g., citric acid, sodium citrate or acetic acid), a suspending agent (e.g., methylcellulose, polyvinylpyrrolidone or aluminum stearate), a dispersing agent (e.g., hydroxypropylmethylcellulose), a diluent (e.g., water), and base wax (e.g., cocoa butter, white petrolatum or polyethylene glycol). The amount of the active ingredient in the medical composition may be at a level that will exercise the desired therapeutical effect; for example, about 0.1 mg to 50 mg in unit dosage for both oral and parenteral administration.

[0050] The active ingredient may be usually administered once to four times a day with a unit dosage of 0.1 mg to 50 mg in human patients, but the above dosage may be properly varied depending on the age, body weight and medical condition of the patient and the type of administration. A preferred dose is 0.25 mg to 25 mg in human patients. One dose per day is preferred.

[0051] Compounds used in the methods invention are readily prepared by the reactions illustrated in the schemes below.

[0052] Certain compounds of formula I are conveniently prepared from an unsaturated intermediate



II

by hydrogenation with a noble metal catalyst in a reaction inert solvent. Pressure and temperatures are not critical and hydrogenation is normally accomplished in a few hours at room temperatures at 20-80 psi hydrogen pressure.

[0053] The hydrogenated product is isolated, purified if desired, and the ether group is cleaved with an acidic catalyst in a reaction inert solvent at a temperature between 0°C to 100°C depending on the acidic catalyst used . Hydrog n bromide at elevated temperatures, boron tribromide and aluminum chloride at 0°C to ambient temperature have been found to b effective for this reaction.

[0054] The product, Formula I is isolated and purified by standard procedures.

[0055] Interm diates of Formula II where A is CH_2, and B, D and E are CH are described in U.S. patent 3,274,213; J. Med. Chem 10, 78 (1967); J. Med. Chem 10, 138 (1967); and J. Med. Chem. 12, 881 (1969), the disclosures of which are herein incorporated by reference. They can also be prepared by procedures described below.

[0056] The preparation of the compounds of Formula I where e=1, A=CH_2, Z^1=OCH_2CH_2, G= cycloalkylamine, B=CH is shown in Scheme 1. Compounds 1-2, where D and E are CH are made by alkylation of 4-bromophenol with the corresponding N-chloroethylamine using potassium carbonate as base in a polar aprotic solvent like dimethylformamide at elevated temperatures. A preferred temperature is 100°C. Compounds 1-2 where D or E or both are N are synthesized using a nucleophilic displacement reaction performed on dibromides (1-1) using hydroxy ethyl cycloalkylamines under phase transfer conditions to afford bromo amines (1-2). Synthesis, 77, 573 (1980). Following halogen metal exchange using n-butyllithium or magnesium metal, bromo amines (1-2) yield the corresponding lithium or magnesium reagents which are allowed to react at low temperature in the presence of cesium chloride preferably (without cesium chloride the reaction also proceeds) with 6-methoxy-1-tetralone to afford either carbinols (1-3) or styrenes (1-4) after acidic workup. Treatment of either carbinols (1-3) or styrenes (1-4) with a brominating agent such as pyridinium bromide perbromide affords bromo styrenes (1-5). Aryl or heteroaryl zinc chlorides or aryl or heteroaryl boronic acids react with bromides (1-5) in the presence of a palladium metal catalyst like tetrakis triphenyl phosphine palladium (0) to yield diaryl styrenes (1-6). [Pure & Applied Chem. 63, 419,(1991) and Bull. Chem. Soc. Jpn. 61, 3008-3010, (1988)] To prepare the preferred compounds the substituted phenyl zinc chlorides or substituted phenylboronic acids are used in this reaction. The aryl zinc chlorides are prepared by quench of the corresponding lithium reagent with anhydrous zinc chloride. The aryl boronic acids, that are not commercially available, are prepared by quenching the corresponding aryl lithium reagent with trialkyl borate, preferably the trimethyl or triisopropyl borate, followed by aqueous acid workup. Acta Chemica Scan. 47, 221-230 (1993). The lithium reagents that are not commercially available are prepared by halogen metal exchange of the corresponding bromide or halide with n-butyl or t-butyllithium. Alternately, the lithium reagent is prepared by heteroatom facilitated lithiations as described in Organic Reactions, Volume 27, Chapter 1. Catalytic hydrogenation of 1-6 in the presence of palladium hydroxide on charcoal, for example, affords the corresponding dihydro methoxy intermediates which were subsequently demethylated using boron tribromide at 0°C in methylene chloride or 48% hydrogen bromide in acetic acid at 80-100°C to afford target structures (1-7). These compounds are racemic and can be resolved into the enantiomers via high pressure liquid chromatography using a column with a chiral stationary phase like the Chiralcel OD columns. Alternately optical resolution can be carried out by recrystallization of the diastereomeric salts formed with optically pure acids like 1,1'-binapthyl-2,2'-diyl hydrogen phosphate (see Example 8).

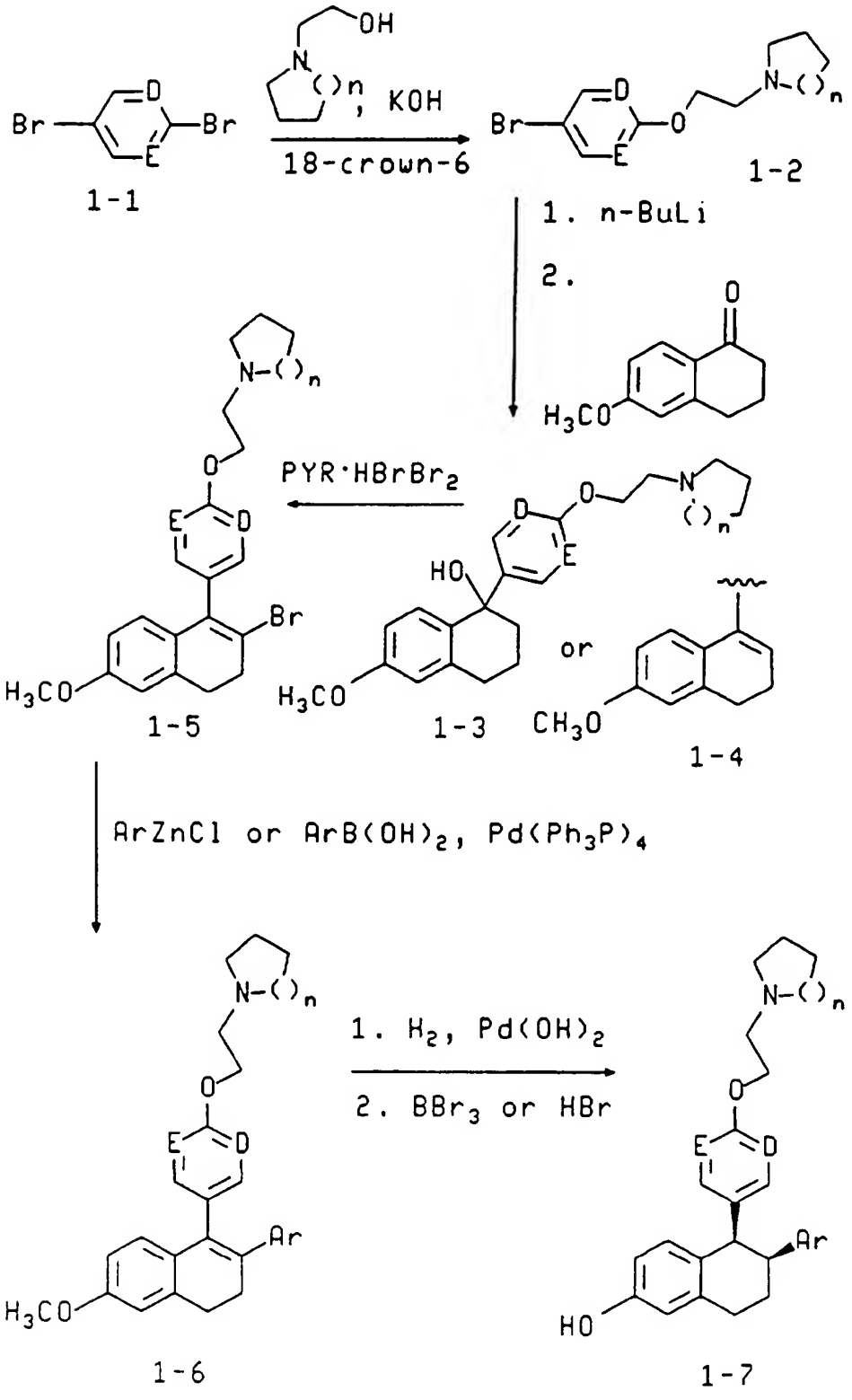
[0057] The cis compounds (1-7) can be isomerized to the trans compounds on treatment with base (see Example 2).

[0058] When D and/or E is nitrogen the intermediates (Formula II) and compounds of Formula I may be prepared from the corresponding dihalopyridines or pyrimidines as illustrated in Scheme 1 and as fully described for 6-phenyl-5-[6-(2-pyrrolidin-1 -yl-ethoxy) pyridin-3-yl]-5,6,7,8-tetrahydronaphthalen-2-ol in Example 6.

[0059] The methyl ether of the compound of Formula I where e=1, A=CH_2, Z^1=OCH_2CH_2, G= pyrrolidine, D,E, B=CH, Y=Ph can also be conveniently prepared by a first step of hydrogenation of nafoxidine (Upjohn & Co., 700 Portage Road, Kalamazoo, MI 49001) in a reaction inert solvent in the presence of a nobel metal catalyst. Pressure and temperature are not critical; the reaction is conveniently run in ethanol at room temperature for approximately 20 hours at 50 psi.

[0060] The second step is cleavage of the methoxy group which is accomplished conveniently at room temperature with an acidic catalyst such as boron tribromide in a reaction inert solvent or at 80-100°C with hydrogen bromide in acetic acid. The product is then isolated by conventional methods and converted to an acid salt if desired.

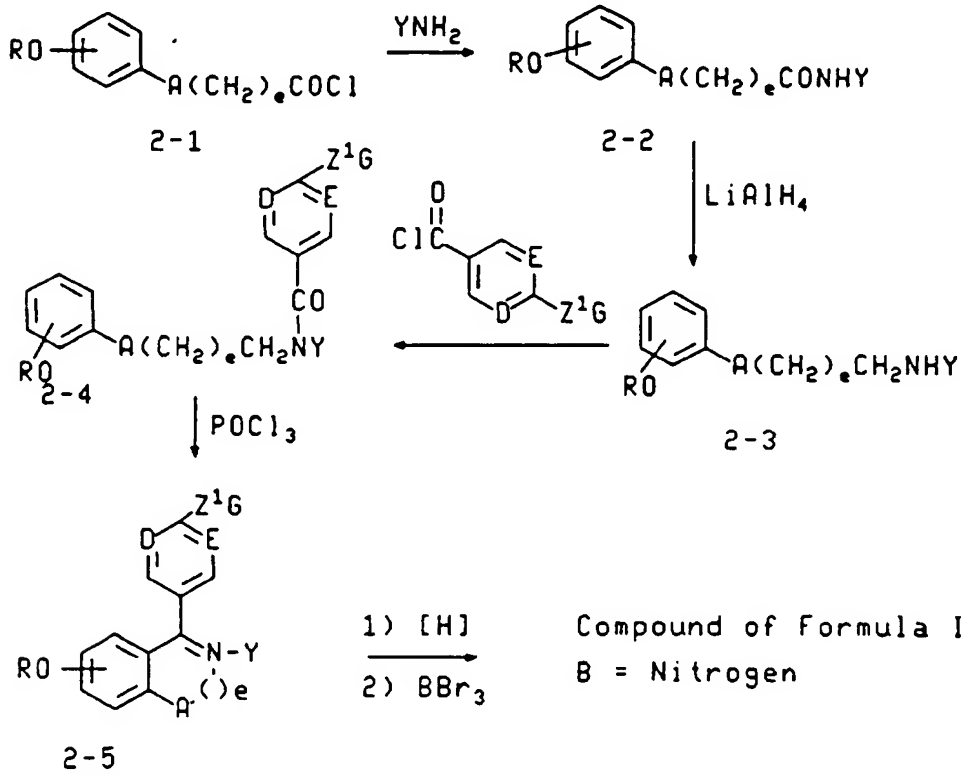
SCHEME 1


OH
N
n
; KOH
18-crown-6
Br
Br
D
E
O
1-1
1-2
1. n-BuLi
2.
H3CO
PYR·HBrBr2
HO
or
CH3O
1-3
1-4
1-5
ArZnCl or ArB(OH)2, Pd(Ph3P)4
1. H2, Pd(OH)2
2. BBr3 or HBr
Ar
1-6
1-7

[0061] Compounds of formula I wherein B is nitrogen are prepared by the procedures illustrated in Scheme 2 and 3 and Examples 3-5 and 10-12.

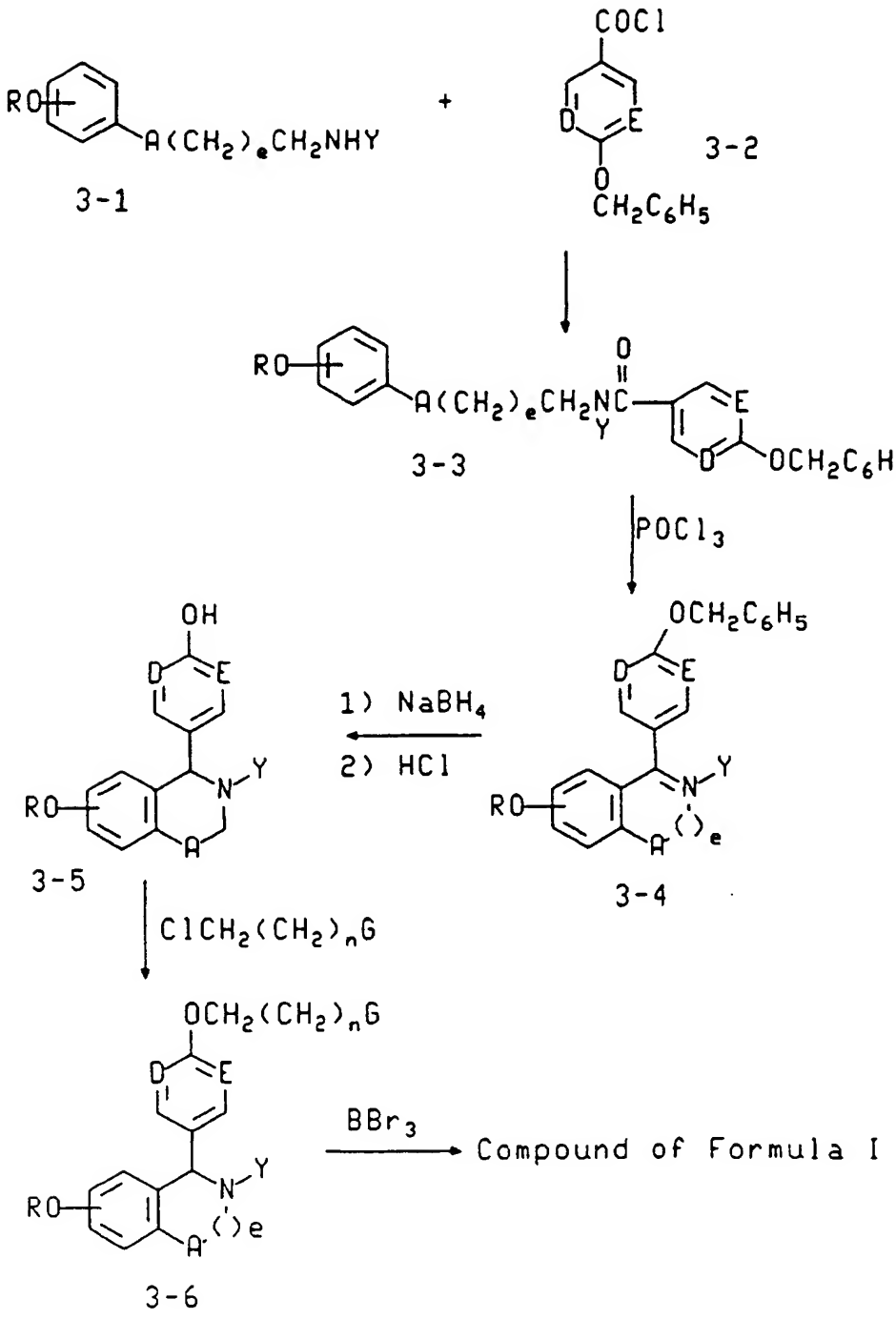
[0062] Th synthesis of compounds of Formula I where B=N is shown in Scheme 2. Aryl acid chlorides (2-1) on treatment with primary amines afford aryl secondary amides (2-2), which are reduced with lithium aluminum hydride in ethereal solvents to yield secondary amines (2-3). Subsequent acylation of (2-3) with aroyl acid chlorides leads to tertiary amides (2-4), which are cyclized in hot phosphorus oxychloride to yield dihydro isoquinolinium salts (2-5). Reduction with sodium borohydride to alkoxytetrahydro isoquinolines; followed by boron tribromide demethylation in methylene chloride affords the target structures.

SCHEME 2



[0063] The synthesis of the compounds of Formula I where B=N is also described below in Scheme 3. Secondary amines (3-1) on acylation with benzyloxyaroyl chlorides (3-2) afford tertiary amides (3-3) which on cyclization with hot phosphorous oxychloride yield dihydro isoquinoline salts (3-4). Sodium borohydride reduction of (3-4) followed by debenzylation with aqueous hydrochloric acid affords isoquinolines (3-5), which are alkylated with the appropriately functionalized chlorides and demethylated with boron tribromide to yield the desired target structures.

SCHEME 3



[0064] Although the free-base form of formula I compounds can be used in the methods of the present invention, it is preferred to prepare and use a pharmaceutically acceptable salt form. Thus, the compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of inorganic and, preferably, organic acids and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkan-

dioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbat , benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate,β-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzenesulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the citrate salt.

[0065] The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

[0066] The pharmaceutically acceptable salts of formula I compounds generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

[0067] Once prepared, the free base or salt form of formula I compounds can be administered to an individual in need of treatment for the methods herein described. The following nonlimiting test examples illustrate the methods of the present invention.

[0068] For the methods of the present invention, compounds of Formula I are administered continuously, or from 1 to 4 times daily.

[0069] As used herein, the term "effective amount" means an amount of compound of the methods of the present invention which is capable of inhibiting the symptoms of the pathological conditions herein described. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the severity of the pathological condition being treated. A typical daily dose will contain a nontoxic dosage level of from about 0.25 mg to about 100 mg/day of a compound of the present invention. Preferred daily doses generally will be from about 1 mg to about 40 mg/day.

[0070] The compounds of this invention can be administered by a variety of routes including oral, rectal, transdermal, subucutaneous, intravenous, intramuscular, and intranasal. These compounds preferably are formulated prior to administration, the selection of which will be decided by the attending physician. Typically, a formula I compound, or a pharmaceutically acceptable salt thereof, is combined with a pharmaceutically acceptable carrier, diluent or excipient to form a pharmaceutical formulation.

[0071] The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation. By 'pharmaceutically acceptable' it is meant the carrier, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

[0072] Pharmaceutical formulations containing a compound of formula I can be prepared by procedures known in the art using well known and readily available ingredients. For example, the compounds of formula I can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following fillers and extenders such as starch, sugars, mannitol, and silicic derivatives binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate agents for retarding dissolution such as paraffin resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

[0073] The compounds also can be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for example, by intramuscular, subcutaneous or intravenous routes.

[0074] Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular physiological location, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

[0075] Compounds of formula I generally will be administered in a convenient formulation. The following formulation examples only are illustrative and are not intended to limit the scope of the present invention.

[0076] In the formulations which follow, 'active ingredient' means a compound of formula I, or a salt thereof.

Formulation 1: Gelatin Capsules

[0077] Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.25-100
Starch, NF	0-650
Starch flowable powder	0-50
Silicone fluid 350 centistokes	0-15

[0078] A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets

[0079]

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Cellulose, microcrystalline	200-650
Silicon dioxide, fumed	10-650
Stearate acid	5-15

[0080] The components are blended and compressed to form tablets.

[0081] Alternatively, tablets each containing 0.25-100 mg of active ingredient are made up as follows:

Formulation 3: Tablets

[0082]

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

[0083] The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° - 60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

[0084] Suspensions each containing 0.25-100 mg of medicament per 5 ml dose are made as follows:

Formulation 4: Suspensions

[0085]

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.25-100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg

(continued)

Ingredient	Quantity (mg/5 ml)
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified Water to	5 mL

[0086] The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume. An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol

[0087]

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

[0088] The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.
Suppositories are prepared as follows:

Formulation 6: Suppositories

[0089]

Ingredient	Quantity (mg/suppository)
Active ingredient	250
Saturated fatty acid glycerides	2,000

[0090] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimal necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

[0091] An intravenous formulation is prepared as follows:

Formulation 7: Intravenous Solution

[0092]

Ingredient	Quantity
Active ingredient	20 mg
Isotonic saline	1,000 mL

[0093] The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 mL per minute.

[0094] Antiestrogens are compounds that prevent estrogens from expressing their effects on estrogen dependent target tissues consequently antagonizing a variety of estrogen-dependent processes. However, most antiestrogents such as tamoxifen are not pure antagonists, since they exhibit some estrogenicity. The methods below enable the skilled practitioner to determine the estrogen and antiestrogen effect of the compounds of this invention. U.S. 4,859,585,

claims two alternative general protocols by which a substance may be characterized as an estrogen agonist and/or estrogen antagonist.

Methods to Determine Estroqenic and Antiestrogenic Potential

[0095] Uterine weight test. Compounds of Formula I are given orally to immatur female Spragu -Dawl y (SD) rats (20 days old; 40 g body wt; Charles River Wiga, Sulzfeld, F.R.G.) for 3 consecutive days to test estrogenic activity. In addition to each dose of a compound of formula I, a standard dose of 1 mg/kg estradiol is administered orally to juvenile SD rats to determine the antiestrogenic effect of the compounds. The compounds are suspended in 0.25% agar for the administration. The animals are killed on day 4, the uteri removed, cleared of any intrauterine fluid and subsequently weighed in a dry condition. Estrogenic activity is estimated by the increase in uterine weight. (uteroptropic effect) initiated by the respective daily doses of compounds of formula 1. The antiestrogenic effect of the compounds is tested by the reduction of the uterine weight (anti uterotropic effect) in the presence of 1 mg/kg estradiol.

[0096] Estrogen receptor-binding assay. Estrogen receptors (ER) are measured in the cytosol of uterine tissue of female immature white New Zealand rabbits (3 months of age). The uteri are separated from surrounding fatty tissue, rinsed in ice-cold phosphate-buffered saline, and immediately transferred Into liquid nitrogen. The frozen uterine tissue is put into a capped Teflon cylinder pre-cooled in liquid nitrogen that is vibrated (501 {7.) for at least 30 sec. in a microdismembrator (Braun, Melsungen, F.R.G.) in the presence of a tungsten carbide bal 1. The resulting power is mixed with units (1:4/w:v) of Trisbuffer (0.01 M '1'r-is, 0.001 EDTA, pH 7.5), homogenized with a Dounce homogenizer and centrifuged at 105,000 g for 1 hr. The supematant (cytosol) is decanted and the protein concentration adjusted to 5 mg protein/ml. The protein concentration is measured according to Lowry et al.[8]. Aliquots of cytosol are pipetted into plastic tubes, 2.5 X 10^{-9}M [17β-^{3}H]estradiol, and a range of concentrations of unlabeled estradiol and antiestrogens of formula I are added. The relative binding affinity of the antiestrogens to the estrogen receptor is carried out with the dextrancharcoal method at 2°C as described by Devleesch ouwer et al. [10].

[0097] All steps are carried out in triplicate. The relative binding affinity is defined as the ratio of the concentrations of radioinert 17β-estradiol to the compound of formula I that is necessary to achieve a 50% inhibition of the specific [17&3 H]estradiol binding. Bound radioactivity at the highest concentration of 17/3 -estradiol (2,5 X 1^{-7}M) is taken as unspecific binding and subtracted from all values.

[0098] Procedures for evaluating compounds of this invention for treatment of skin and vaginal atrophy are described in U.S. Patent 5,461,064.

Skin Atrophy [for illustrative purposes only]

[0099] Three to twenty women, who are post-menopausal and in good health, are selected. Additionally, these women are selected on the basis of their presenting several signs of rapid dermal atrophy, such as a rapid increase in the number of facial wrinkles or crow's feet, rapid change in the pigmentation of the skin, I.e. "age spots", or other complaints of rapid dermal aging. It should be remembered by the attending physician that these criterion may be highly subjective to the patient and that some consideration must be taken into account in patient selection. Also, dermal atrophy may be the result of other factors such as UV damage from the sun or other environmental insults and that such patients who are suffering from these effects would be excluded.

[0100] The first component of the study is qualitative and subjective one, i.e., an evaluation of improvement in the patient's appearance. Such an evaluation requires an initial benchmark for future comparison. Some initial benchmarks might be in the form of a standardized set of questions as to how the patient views her own appearance, photographs of the patient, or a psychological profile of the patient's self-image. The second component is quantitative; these include the measurement of urinary excretion of hydroxyproline, moisture content of the skin, glycosaminoglycans in the skin, and changes in resilience and pliability of the skin. Methods for determining these factors are found in 'The Menopause', Ed. R.J. Beard, University Press, Chapter 7 (1977) and 'Methods in Skin Research', Ed. Skerrow, D. and Skerrow C. J., John Wiley & Sons Ltd., Chp. 22, 'Analysis of Sebaceous Lipids", p. 587-608 (1985), and further references cited therein, all herein incorporated by reference. Again, an initial benchmark of these quantitative factors is obtained.

[0101] The women, thus selected and initially evaluated, are placed in a clinical protocol of receiving 20-100 mg of a compound of this invention by oral administration either as a single or split dose. Alternatively, these patients are placed in a protocol for topical administration to areas of the skin most effected by the atrophy. This topical protocol includes the use of a suitable formulation containing 5-50% (by weight) of an active compound of this invention applied to the affected area once or twice a day. Either of these protocols continues two to twelve months. Subsequ nt evaluations, both quantitative and qualitative, are made at appropriate intervals.

[0102] A positive result is an improvement in the overall qualitative index of the patient's appearance and/or an improvement in the quantitative parameters, e.g., an increase in the urinary excretion of hydroxyproline signifying an increase in turnover and synthesis of collagen, an increase in moisture content, glycosaminoglycans, pliability, or re-

silience of the skin.

Vaginal Atrophy [For illustrative purposes only]

[0103] Three to twenty women suffering from vaginal atrophy associated with menopause are selected. These women are in general good health. Since the nature of this disorder is highly idiosyncratic and subjective, valuation of the effectiveness of treatment would necessarily be subjective in nature. These patients are asked to keep a daily log noting such details as vaginal itching and scaling and the degree of comfort in sexual intercourse. These women are placed on a clinical protocol similar to that described above for atrophy of the skin. Particular emphasis is placed on the use of vaginal suppositories containing 5-25% of an active compound of this invention.

[0104] A positive result is an improvement in the comfort of sexual intercourse and/or a decrease in vaginal itching or scaling.

[0105] Utility of the compounds described herein is exhibited by the positive results observed in one or both of the above assays.

[0106] Procedures for evaluating the utility of a compound of this invention for increasing the libido of post-menopausal women are described in United States Patent 5,439,931.

Assay 1

[0107] Animals used are ovariectomized or ovariectomized/adrenalectomized Sprague-Dawley rats (Specific Pathogen Free-Anticimex, Stockholm) weighing 250-300 gms. They are housed in a room maintained at a temperature of 24°C under reversed lighting (10 hours dark). Food and water (or saline) are available ad libitum. A compound of the invention is administered to one group of rats, and the other group is maintained as a control, and behavioral observations are made by placing each female with 2 cage-adapted, sexually experienced males for a 5-minute period during which about 20 mounts occur. The following measures are recorded:

1. Proportion of mounts by the male which elicited a lordosis response - L/M;
2. Lordosis intensity measured on a 3 point scale;
3. Lordosis duration (in seconds);
4. Female acceptance ratio - No. of mounts divided by No. of refused mounting attempts plus mounts, a measure of the female's willingness to accept the male when he attempts to mount her.

[0108] Activity of the compound Is shown through positive impact on any one of the 4 observations, as compared to control.

Assay 2

[0109] Five to fifty women are selected for the clinical study. These women are post-menopausal, i.e., have ceased menstruating for between 6 and 12 months prior to the study's initiation, are in good general health, and suffer from self-described loss of libido especially noted after menopause. Because of the idiosyncratic and subjective nature of this symptom, the study has a placebo control group, i.e., the women are divided into two groups, one of which receive the active agent of this invention and the other receives a placebo. Women in the test group receive between 50-200 mg of the drug per day by the oral route. They continue this therapy for 3-12 months. Accurate records are kept as to the level of libido of the women In both groups and at the end of study these results are compared.

[0110] Activity of the compounds of the invention is illustrated by positive effects in at least one of the above assays.

[0111] Procedures for determining the effectiveness of compounds of this invention in treatment of pulmonary hypertensive disease are described in U.S. Patent 5,447,941.

Assay 1

[0112] The procedure as set out in Farhat et al., J PET, 261: 686 (1992) (herein incorporated by reference) is carried out. Four to thirty rats are sacrificed. The lungs are exsanguinated by perfusion via the hepatic pulmonary vein. The pulmonary artery is cannulated as is the trachea to maintain ventilation and the pulmonary cannula is connected to the perfusion line and the whole ventilated lung is removed and suspended in a perfusion chamber. The effects of vasoconstrictor substances on perfusion pressure of the isolated perfused lung is measured using a Statham pressure transducer. The increase in perfusion pressure (vasoconstriction) induced by thromboxane mimetics in the presence of estradiol is determined and the ability to block the thromboxane effects with a compound of formula I or the estradiol potentiation of the thromboxane effects will be determined.

[0113] Activity of compounds of formula I is illustrated by a reduction in pulmonary perfusion pressure increase following thromboxane mimetic stimulation.

Assay 2

[0114] Between five and fifty rats are administered a single IV dose of monocrotaline pyrrole, (3.5 mg/kg) and pulmonary disease is evaluated by histopathology, accumulation of fluorescein conjugated dextran in bronchial alveolar lavage fluid (as a measurement of pulmonary edema), and measurement of artery pressure using a Standtham P231D pressure transducer (Reindel et al., Tax and Applic. Pharm. 106:179-200 (1990). A compound of formula I is administered and the effect on the rats are evaluated.

[0115] Activity of compounds of formula I is illustrated by a reduction in uptake of fluorescein conjugated dextran from bronchial alveolar lavage fluids of animals treated with a compound of formula I, indicating a reduction in pulmonary edema. Rat lungs will also be removed from thorax, perfused with modified Karnovskys fixative and processed for histopathology. A reduction in thickening of the arterial walls in treated rats is evidence for the protective role of compounds of formula I as is a decrease in pulmonary artery pressure.

Assay 3

[0116] Five to fifty women are selected for the clinical study. The women suffer from a pulmonary hypertensive disease. Because of the idiosyncratic and subjective nature of these disorders, the study has a placebo control group, i.e., the women are divided into two groups, one of which receives a compound of formula I as the active agent and the other receives a placebo. Women in the test group receive between 50-200 mg of the drug per day by the oral route. They continue this therapy for 3-12 months. Accurate records are kept as to the number and severity of the symptoms in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the symptoms reported by each patient before the study began.

[0117] Utility of the compounds of formula I is illustrated by the positive impact they have in at least one of the assays described above.

[0118] The utility of a compound of this Invention for inhibiting seborrhea is tested by the procedures described in U.S. Patent 5,439,923.

Assay 1

[0119] Each of from between two and twenty patients selected for the clinical evaluation is placed in a comfortable environment, i.e., comfortable temperature, humidity, lighting, etc. These patients have refrained from strenuous exercise and consumption of spicy foods for the twelve hours prior to the evaluation. An area of the body which contains a large number of sebaceous glands affected by seborrhea or acne, such as the forehead, is wiped with a gauze pad to remove accumulated lipids. A patch of the skin is taped off, forming a rectangle sized 2.5 by 1.8 cm. A pad of cigarette paper or other suitable absorbent material sixed 2.5 by 1.8 cm Is placed on the test area of the skin. The absorbent material must have first been defatted with ether prior to the placement on the test area to remove background lipids. The pad is the held in place with a bandage. After fifteen minutes the pad is replaced with a fresh pad (test pad). This procedure removes the background lipids in the skin so the true rate of lipid production by the sebaceous glands may be determined. The test pad is left in place for three to six hours and then removed. The test pad is then extracted with ether to remove the lipids and the ether evaporated. The residual lipids are then weighed. The result is expressed as the number of sebaceous lipids (mg) per 10 cm^2 per hour. The patient then takes either 30-400 mg/day of the active ingredient by the oral route, or applies a topical formulation containing 5-20% by weight of the active ingredient daily, both for three to nine weeks. The above described test pad methodology is repeated several times throughout administration of the active ingredient to monitor progress. This assay may also be performed on animals to verify utility. A positive effect is reflected by a decrease of the rate of sebaceous gland lipid production.

Assay 2

[0120] Between two and twenty patients are enrolled in this clinical protocol and are initially evaluated by direct observation of the skin and lesions thereon. This is done by choosing one cm^2 sections of affected skin and the number and type of lesion (comedos, seborrheic lesions, etc.) is noted. The areas normally used are the cheeks, scalp or back. The patient then takes either 30-400 mg/day of the active ingredient by the oral route, or applies a topical formulation containing 5-20% by weight of the active ingredient daily, both for three to nine weeks. The areas of the skin being evaluated are checked during the period of administration. Care must be taken to evaluate the same areas and in order

to accomplish this, a small mark or marks may be made on the skin by a permanent marker. A positive result is reflected by a reduction in the number and/or severity of the lesions in the monitored areas of the skin.

[0121] Utility of the compounds described herein is exhibited by the positive results observed in one or both of the above assays.

[0122] Utility of the compounds of this invention for treating Turner's Syndrome is determined by a procedure described in U.S. Patent 5,441,966.

Test Procedure

[0123] Five to thirty females are selected for the clinical study. The females are between the age of twelve and eighteen and exhibit characteristics of Turner's Syndrome, but are in good general health otherwise. The study has a placebo control group, i.e., the females are divided into two groups, one of which receives the active agent of this invention and the other receives a placebo. Females in the test group receive between 10-100 mg of the active agent per day by the oral route. They continue this therapy for 3-12 months. Accurate records are kept as to the number and severity of the above mentioned symptoms in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the symptoms reported by each patient before the study began.

[0124] Utility of the compounds of the invention is illustrated by the positive impact they have on one or more of the symptoms when used in a study as above.

[0125] EP 0 659 419 A1 provides methods for evaluating compounds of the present invention for breast disorders.

Assay 1

[0126] Five to fifty women are selected for the clinical study. The women have a history of a breast disorder as described herein, but are in good general health. Because of the subjective nature of these disorders, the study has a placebo control group, i.e., the women are divided into two groups, one of which receive the active agent of this invention and the other receive a placebo. Women in the test group receive between 50-200 mg of the drug per day by the oral route. They continue this therapy for 3-12 months. Accurate records are kept as to the status of the breast disorders in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the symptoms reported by each patient before the study began.

[0127] Utility of the compounds of the invention is illustrated by the positive impact they have on the disorder or a symptom or symptoms thereof when used in a study as above.

Assay 2

[0128] Between three and twenty male patients suffering from gynecomastia or galactorrhea are selected. Initial measurement of breast size and evidence of lactation is noted. The patients receive 30-100 mg of an active compound of this invention per day as a single or divided dose via the oral route. This treatment is continued for 3-12 months. At appropriate intervals, further measurements of breast size or evidence of lactation are being made.

[0129] Utility of the compounds of the invention is illustrated by the positive impact on the disorder or its symptoms.

[0130] A method for determining hypoglycemic activity of the compounds of this invention is set forth in EP 0 635 264 A2.

[0131] Five to 6 month old male, inbred viable yellow obese-diabetic mice are used. Male viable yellow mice are obese, hyperglycemic, hyperinsulinemic and insulin resistant.

[0132] Mice are housed 6 per plastic cage with bedding and fed water and Purina Formulab Chow 5008 (Purina Mills, St. Louis, MO) ad libitum. The temperature of the animal rooms is maintained at 23 ± 2°C. Lights in the animal rooms were on from 0600 to 1800 h.

[0133] Antiestrogens are tested at various doses as admixtures of diets. Each dose of an antiestrogen is tested on 6 mice housed in the same cage. Compounds are mixed in pulverized chow and repelletized. Mice serving as controls are given repelletized diet without any test compound. Blood samples are collected from the tail vein immediately before and weekly after the start of a test. Blood glucose concentrations are determined by the glucose oxidase method with a model 300 Alpkem Rapid Flow Analyzer (Clackamaus, OR).

[0134] Reduction of blood glucose concentration below the levels of the control is indicative of an effective antiestrogen with utility in treatment of diabetes and hyperglycemia.

[0135] Methods for evaluating the effect of compounds of this invention in treating obsessive-compulsive are described in EP 0 659 428 A1.

Assay

[0136] Five to fifty women are selected for the clinical study. The women are post-menopausal, i.e., have ceased menstruating for between 6 and 12 months prior to the study's initiation, are in good general health, and suff r from either obsessive-compulsive or a consumptive disorder. Because of the idiosyncratic and subjective nature of these disorders, the study has a placebo control group, i.e., the women are divided Into two groups, one of which receives raloxifene as the active agent and the other receives a placebo. Women in the test group receive between 50-200 mg of the drug per day by the oral route. They continue this therapy for 3-12 months.

[0137] Accurate records are kept as to the number and severity of the symptoms In both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the symptoms reported by each patient before the study began.

[0138] Utility of the compounds of formula I is illustrated by the positive impact they have on one or more of the disorders/symptoms when used in the assay described above.

[0139] EP 0 659 414 A2, describes methods for evaluating compounds of the invention for inhibition of alopecia.

Alopecia

[0140] Three to twenty women suffering from female pattern alopecia are selected. These patients are initially scored for the extent and severity of the alopecia. This clinical evaluation is made by the methods described in "Methods of Skin Research," John Wiley and Sons, pp 308-318 (1985) and Habif, T., 'Clinical Dermatology,' C. V. Mosby Co., Chapter 23, pp 493-504 (1985); and references therein. Especially helpful in these evaluations is the 'hair pluck' procedure and measurement of anagen to telogen ratio. The patients receive 10400 mg of an active compound of this invention per day as a single or split dose by oral administration. Alternatively, the patients apply a 5-10% (by weight of a compound of this invention) as a creme, lotion, or shampoo to the affected area, once to twice a day. This protocol continues for six months. At appropriate intervals, re-evaluation by one of the methods described in the above references is made. A positive result is exhibited by an increase in the anagen to telogen ratio or an increase in the number of terminal hairs in the affected scalp region.

[0141] Utility of the compounds of the invention is illustrated by the positive impact they have on one or more of the symptoms when used in a study as above.

[0142] Assays which show the ability of compounds of the invention to increase macrophage function are described in EP 0 659 425 A1.

Assay 1

[0143] The procedure as set out in Friedman et al., J. Clin. Invest., 75, 162-167 (1985) (herein incorporated by reference) is carried out, with certain modifications. Between five and one hundred mice are administered oral doses in the range of 1-10 mg/kg of a compound of formula 1 on a daily basis. Following the administration, macrophages are harvested and changes in both immune (Fc mediated) and non-immune phagocytosis are quantitated by using fluorescein conjugated yeast particles prepared based on Ragsdale, J. Immunol. Meth., 123:259 (1989). For immune mediated phagocytosis, fluorescein conjugated yeast is preincubated with mouse sera to promote opsonization. Increase in fluorescence uptake by macrophages is quantitated by an increase in fluorescent emission using excitation and emission wavelengths of 482 and 520 nm, respectively. This procedure is used with ex vivo or in vitro macrophage cultures and changes in fluorescence units quantitated.

[0144] An increase in fluorescent units, as compared to control indicates activity of compounds of formula 1.

Assay 2

[0145] The procedure as set out in Zuckerman et al., Cell immunol, 103:207, (1986); J. Immunol., 140:978 (1988) (herein incorporated by reference) is carried out. The ability to induce class II antigens and consequently promote antigen presentation is determined on ex vivo primary peritoneal macrophages and in vitro with the murine macrophage cell line P388D1. Between five and one hundred mice are dosed with a compound of formula 1 macrophages are harvested and probed with antibodies against class II antigens of the D haplotype. Increased class II antigen expression is determined by flow cytometry using the appropriate secondary antibodies. In vitro studies evaluate the effects of the compounds in increasing the basal level and gamma interferon inducible expression of class II antigen by flow cytometry. An increase in class II expression reflect an increase in macrophage activation.

Assay 3

[0146] The procedure as set out in Seow et al., J. Immunol. Meth., 98, 113 (1987) is carried out. The assay is used to evaluate increases in macrophage effector functions which uses measurements of 2-deoxyglucose uptake. Macrophages ex vivo and in vivo are plated in 96 well plates at 10^5 cells per well and incubated in phosphate buffered saline in the presence of 0.78 uCi/ml of 3H-deoxyglucose, and a compound of formula 1 is placed in the wells. Reduction in the amount of extracellular glucose reflects the uptake of this non-metabolizable glucose analog and consequently provides an independent assay for the determination of the state of macrophage activation mediated by the compound of formula 1. Increase in deoxyglucose uptake by the compound demonstrates the ability of the compounds to increase the state of macrophage activation.

Assay 4

[0147] The procedure as set out in Zuckerman, Circ Shock, 29, 279 (1989) (herein incorporated by reference) is carried out to illustrate the ability of the compounds of formula 1 to protect in murine sepsis and endotoxin lethality models. Between five and one hundred mice are dosed orally with 1-10 mg/kg with a compound of formula 1 for 1 week prior to sepsis challenge. Challenge is performed using a bolus IV endotoxin injection under condition in which an LD100 is achieved (200 μg lipopolysaccharide). Exogenous glucocorticoids such as dexamethasone at 20 mg/kg serve as a positive control in creasing survival. The effects of the compound of formula 1 is also determined using a sepsis model involving cecal ligation and puncture. Sepsis by both Gram positive and Gram negative organisms results in an LD100 by 48 hours despite the use of antibiotics. An increase in the number of surviving animals or in survival time, as compared to control, demonstrates the activity of the compounds.

Assay 5

[0148] The ability of the compounds of formula 1 to increase the secretion of cytokines such as TNF is quantitated in vivo by sera measurements using commercially available TNF EUSAs specific for mouse TNF. Between five and one hundred mice are orally dosed with 1-10 mg/kg of a compound of formula 1 for one week prior to injection of a lethal or sublethal dose of lipopolysaccharide (200 and 1 μg, respectively). At one hour post LPS injection the mice are bled and the basal and LPS inducible amounts of serum TNF determined. Routinely, TNF levels below 10 pg/ml are observed prior to LPS injection and achieve levels of 5-20 ng/ml following LPS. The ability of the compounds to modulate the basal or inducible levels of TNF is determined. An increase in basal TNF without triggering massive systemic TNF release in compound treated mice demonstrates the activity of the compounds in promoting cytokyne secretion. Finally, ex vivo and in vitro measurements of TNF release from peritoneal macrophages exposed to 1-5 μM of a compound in vitro is also performed by EUSA to determine the extent of cytokine increase mediated by a compound of formula 1.

Assay 6

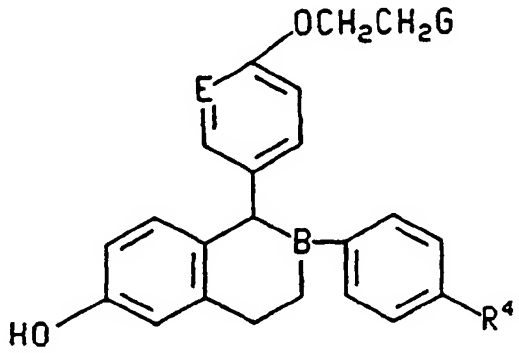
[0149] Five to fifty women are selected for the clinical study. The women are immunosuppressed. Because of the idiosyncratic and subjective nature of these disorders, the study has a placebo control group, i.e., the women are divided into two groups, one of which receives a compound of formula 1 as the active agent and the other receives a placebo. Women in the test group receive between 50-200 mg of the drug per day. They continue this therapy for 3-12 months. Accurate records are kept as to the number and severity of the symptoms in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the symptoms reported by each patient before the study began.

[0150] Utility of the compounds of formula 1 in increasing macrophage function is illustrated by the positive impact they have in at least one of the assays described above. Such compounds are useful in combating infections and promote wound healing.

Claims

1. The use of a compound of the formula I, or of an optical or geometric isomer thereof; or of a non-toxic pharmacologically acceptable acid addition salt, N-oxide, ester or quaternary ammonium salt thereof, for the manufacture of a medicament for inhibiting a pathological condition which is susceptible or partially susceptible to inhibition by an estrogen, antiestrogen or estrogen agonist, said pathological condition being selected from uterine cancer, migraine, incontinence, bladder infection, senile gynecomastia, diabetes, hyperglycemia, failure of wound healing,

melanoma, impotence, inflammatory bowel disease, decreased libido, immune system disorders pulmonary hypertensive disease, seborrhea. Turner's syndrome, alop cia and obsessive-compulsive disorders :-



I

wherein G is

and
R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N.

2. The use according to Claim 1 wherein the compound of formula I is selected from the group consisting of

Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol,
(-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol,
Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalen-2-ol,
Cis 1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene,
1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline,
Cis-6-(4'hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, and
1-(4'-Pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

3. The use according to claim 1 wherein said pathological condition is a bladder infection.

4. The use according to claim 1 wherein said pathological condition is senile gynecomastia.

5. The use according to claim 1 wherein said pathological condition is diabetes.

6. The use according to claim 1 wherein said pathological condition is hyperglycemia.

7. The use according to claim 1 wherein said pathological condition is failure of wound healing.

8. The use according to claim 1 wherein said pathological condition is decreased libido.

9. The use according to claim 1 wherein said pathological condition is an immune system disorder.

10. The use according to claim 1 wherein said pathological condition is pulmonary hypertensive disease.

11. The use according to claim 1 wherein said pathological condition is seborrhea.

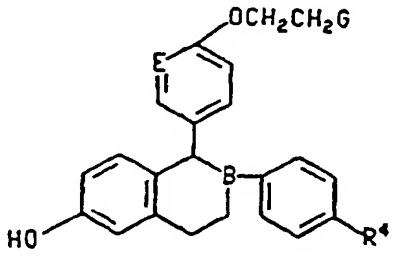
12. The use according to claim 1 wherein said pathological condition is Turner's Syndrome.

13. The use according claim 1 wherein said pathological condition is alopecia.

14. The use according to claim 1 wherein said pathological condition is an obsessive-compulsive disorder.

Patentansprüche

1. Verwendung einer Verbindung der Formel I oder eines optischen oder geometrischen Isomers davon; oder eines nicht toxischen pharmakologisch verträglichen Säureadditionssalzes, N-Oxids, Esters oder quaternären Ammoniumsalzes davon zur Herstellung eines Arzneimittels zur Hemmung eines pathologischen Zustands, der für eine Hemmung durch ein Östrogen, Antiöstrogen oder einen Östrogenagonisten anfällig oder teilweise anfällig ist, wobei der pathologische Zustand aus Uteruskrebs, Migräne, Inkontinenz, Blaseninfektion, seniler Gynäkomastie, Diabetes, Hyperglykämie, Wundheilungsstörung, Melanom, Impotenz, entzündlicher Darmerkrankung, verminderter Libido, Störung des Immunsystems, pulmonaler hypertensiver Erkrankung, Seborrhoe, Turners Syndrom, Alopezie und obsessivenzwanghaften Störungen ausgewählt ist:



I

wobei G

ist; und

R^4 H, OH, F oder Cl darstellt; und B und E unabhängig voneinander aus CH und N ausgewählt sind.

2. Verwendung nach Anspruch 1, wobei die Verbindung der Formel I ausgewählt ist aus der Gruppe, bestehend aus

cis-6-(4-Fluor-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphth-2-ol;
(-)-cis-6-Phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphth-2-ol;
cis-6-Phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphth-2-ol;
cis-1-[6'-Pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalin;
1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorphenyl)-6-hydroxy-1,2,3,4-tetrahydroisochinolin;
cis-6-(4'-Hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphth-2-ol und
1-(4'-Pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisochinolin.

3. Verwendung nach Anspruch 1, wobei der pathologische Zustand eine Blaseninfektion ist.

4. Verwendung nach Anspruch 1, wobei der pathologische Zustand senile Gynäkomastie ist.

5. Verwendung nach Anspruch 1, wobei der pathologische Zustand Diabetes ist.

6. Verwendung nach Anspruch 1, wobei der pathologische Zustand Hyperglykämie ist.

7. Verwendung nach Anspruch 1, wobei der pathologische Zustand eine Wundheilungsstörung ist.

8. Verwendung nach Anspruch 1, wobei der pathologische Zustand eine verminderte Libido ist.

9. Verwendung nach Anspruch 1, wobei der pathologische Zustand eine Störung des Immunsystems ist.

10. Verwendung nach Anspruch 1, wobei der pathologische Zustand eine pulmonale hypertensive Erkrankung ist.

11. Verwendung nach Anspruch 1, wobei der pathologische Zustand Seborrhoe ist.

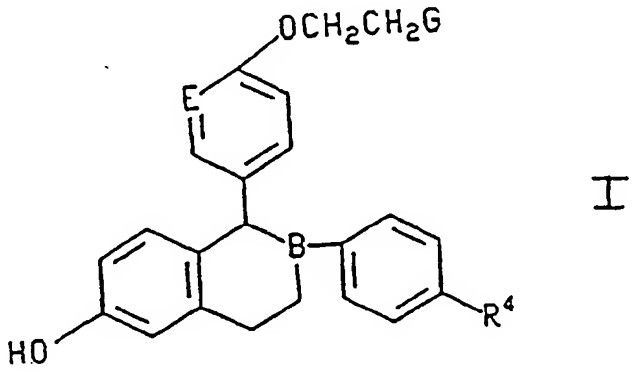
12. Verwendung nach Anspruch 1, wobei der pathologische Zustand Turners Syndrom ist.

13. Verwendung nach Anspruch 1, wobei der pathologische Zustand Alopezie ist.

14. Verwendung nach Anspruch 1, wobei der pathologische Zustand eine obsessive-zwanghafte Störung ist.

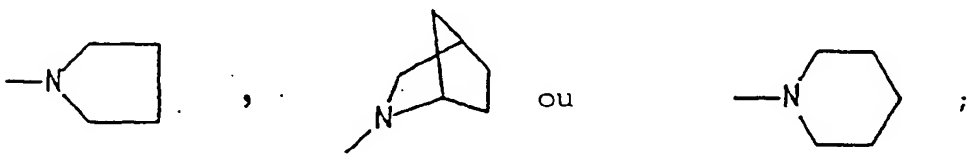
Revendications

1. Utilisation d'un composé de formule I ou d'un de ses isomères optiques ou géométriques, ou bien d'un de ses sels d'addition d'acides, N-oxydes, esters ou sels d'ammonium quaternaires non toxiques pharmacologiquement acceptables, pour la production d'un médicament destiné à inhiber un état pathologique qui est sensible ou partiellement sensible à l'inhibition par un oestrogène, un anti-oestrogène ou un agoniste d'oestrogène, ledit état pathologique faisant partie du groupe comprenant le cancer de l'utérus, la migraine, l'incontinence, une infection de la vessie, la gynécomastie sénile, le diabète, l'hyperglycémie, le défaut de cicatrisation de plaies, un mélanome, l'impuissance, une maladie intestinale inflammatoire, une diminution de la libido, une perturbation du système immunitaire, un état d'hypertension pulmonaire, la séborrhée, le syndrome de Turner, l'alopécie et les troubles obsessionnels compulsifs :



I

formule dans laquelle G représente un groupe



et
R^4 représente H, un groupe OH, F ou Cl ; et B et E sont choisis indépendamment entre un groupe CH t N.

2. Utilisation suivant la revendication 1, dans laquelle le composé de formule I est choisi dans le groupe consistant en les suivants :

cis-6-(4-fluorophényl)-5-[4-(2-pipéridine-1-yl-éthoxy)-phényl] -5,6,7,8-tétrahydro-naphtalène-2-ol,
(-)-cis-6-phényl-5-[4-(2-pyrrolidine-l-yl-éthoxy)-phényl]-5,6,7,8-tétrahydro-naphtalène-2-ol,
cis-6-phényl-5-[4-(2-pyrrolidine-1-yl-éthoxy)-phényl]-5,6,7,8-tétrahydro-naphtalène-2-ol,
cis-1-[6'-pyrrolidinoéthoxy-3'-pyridyl]-2-phényl-6-hydroxy-1,2,3,4-tétrahydronaphtalène.
1-(4'-pyrrolidinoéthoxyphényl)-2- (4"-fluorophényl)-6-hydroxy-1,2,3,4-tétrahydro-isoquinoléine,
cis-6-(4'-hydroxyphényl)-5-[4-(2-pipéridine-l-yl-éthoxy)-phényl]-5,6,7,8-tétrahydro-naphtalène-2-ol, et
1-(4'-pyrrolidinoéthoxyphényl)-2-phényl-6-hydroxy-1,2,3,4-tétrahydro-isoquinoléine.

3. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est une infection de la vessie.

4. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est la gynécomastie sénile.

5. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est le diabète.

6. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est une hyperglycémie.

7. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est un défaut de cicatrisation de plaies.

8. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est une diminution de la libido.

9. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est un trouble du système immunitaire.

10. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est un état d'hypertension pulmonaire.

11. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est la séborrhée.

12. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est le syndrome de Turner.

13. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est l'alopécie.

14. Utilisation suivant la revendication 1, dans laquelle l'état pathologique est un trouble obsessionnel compulsif.